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Association of diurnal temperature range with daily mortality in England and Wales: A nationwide time-series study

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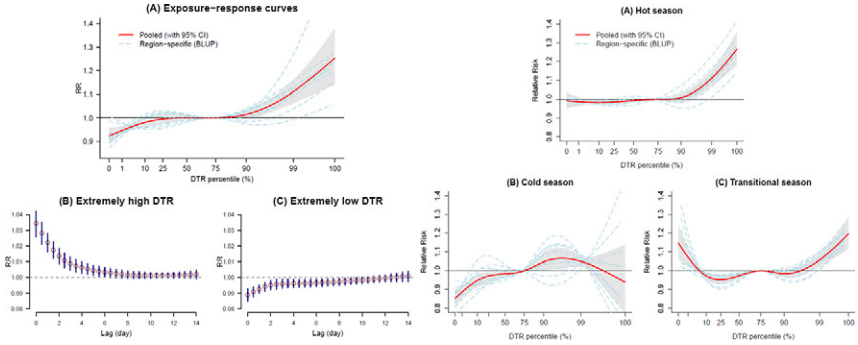
HIGHLIGHTS

- A nationwide investigation of fourteen-year time-series data
- A nonlinear DTR-mortality association was identified with distinct seasonal patterns.
- Extremely high DTR increased short-term mortality, whereas extremely low DTR exhibited entirely different seasonal effects.
- Mortality vulnerability to DTR extremes varied greatly by regional latitudes and climate conditions.
- Findings are important for public health decision-making in coping with climate change.

GRAPHICAL ABSTRACT

Left panel: Pooled exposure-response relationship and lag patterns of extremely high and low DTR.
Right panel: Pooled and region-specific DTR-mortality associations stratified by season.



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ABSTRACT

Background: Diurnal temperature range (DTR) reflects within-day temperature variability and is closely associated with climate change. In comparison to temperature extremes, up-to-date DTR-health evidence at the regional and national scales has been still very limited worldwide, especially in Europe.
Objectives: This study aimed to provide nationwide estimates for DTR-associated effects on mortality, and explore whether season and regional-level characteristics modify DTR-mortality relation in United Kingdom.
Methods: Fourteen-year time-series data on weather and mortality were collected from 10 regions in England and Wales during 1993–2006, including 7,573,716 total deaths. A quasi-Poisson regression incorporated with distributed lag non-linear model was first applied to estimate region-specific DTR-mortality relationships. Then, a multivariate meta-analysis was employed to derive the pooled DTR effects at the national level. Also, the modifying effects of some regional characteristics (e.g., geographical and climatological) were examined by conducting multivariate meta-regression.
Results: A non-linear DTR-mortality relationship was identified in UK. At the national level, increasing DTR raised the mortality risk observably when DTR exposure was below 25th percentile or above 90th percentile of DTR distribution, with an intermediate risk plateau indicating no associations. Extremely high DTR exhibited greater adverse effect estimates in hot season compared with in cold and transitional season, whereas entirely different association patterns were observed for the season-specific effects of extremely low DTR. In addition to season, regional latitudes, average temperature and humidity were also found to significantly modify DTR-mortality relationship.

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Conclusions: Our study added strong evidence that extremely high DTR increased short-term mortality, whereas the effects of extremely low DTR exhibited entirely different seasonal patterns. Also, mortality vulnerability to DTR extremes varied greatly by regional latitudes and climate conditions.

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1. Introduction

Over the past decades, climate change has raised increasing research interests in weather-related health assessment. Temperature extremes, namely cold, heat or both, have been extensively linked with a wide variety of health consequences throughout our lives (Onozuka and Hagihara 2017; Song et al. 2017; Ye et al. 2012; Zhang et al. 2017c; Zhao et al. 2017). As shown in large bodies of epidemiologic studies, increased mortality burden arising from non-optimum temperature exposure remains a great public health threat across the globe (Gasparrini et al. 2015b; Hajat et al. 2010). The observed temperature-mortality relationships varied greatly by regions and climates, generally with U, V, or J-patterns (Gasparrini et al. 2015b; Guo et al. 2014; Ma et al. 2015a). Furthermore, heat effects tended to appear immediately and only persisted for several days, whereas cold effects were delayed and lasted for weeks (Guo et al. 2014; Zhang et al. 2017a).

In addition to heat and cold, unstable weather is an emerging environmental trigger for extra health risks. In some countries/regions, for instance, significant short-term associations of health with temperature changes during a certain period have been reported for cause-specific mortality (Lim et al. 2015; Zhan et al. 2017; Zhang et al. 2017b; Zhou et al. 2014) and hospital admissions (Liang et al. 2009; Lichtman et al. 2016; Lim et al. 2012a; Qiu et al. 2015; Teng et al. 2013). Also, two population-based cohort studies suggested the harmful effects on long-term survival in relation to within-season temperature variability (Shi et al. 2015; Zanobetti et al. 2012). These growing epidemiologic findings highlighted the significant role of unstable temperatures in influencing health, suggesting the great potential health benefit for the public to take some preventive and interventional actions in coping with large changes of regional climates.

Defined as the difference of maximum and minimum temperature within a day, diurnal temperature range (DTR) reflects daily temperature variability and is closely associated with climate change in regions such as European areas (Makowski et al. 2008; Yang et al. 2013). In recent years, the adverse impact of high DTR exposure has been identified in a growing number of time-series studies, while showing great differences in effect estimates and seasonal patterns (Cheng et al. 2014; Ding et al. 2015; Lim et al. 2012b; Luo et al. 2013). However, most available evidence was based on single-city investigations or limited within some developed metropolises, and relatively comprehensive understandings of DTR-health relation were thus very limited at the regional and national scales (Kim et al. 2016). Additionally, in comparison to temperature extremes, DTR-related health effects have been still less studied worldwide and worse understood in diverse climate zones, especially in Europe (Cheng et al. 2014).

In this study, we thus conducted a large-scale observational investigation covering all regions of England and Wales, aiming to provide nationwide estimates for DTR-associated effects on mortality, and explore whether season and regional-level characteristics modify DTR-mortality relation in UK.

2. Materials and methods

2.1. Weather and mortality data

We collected the 14-year time-series data on weather and mortality covering 10 UK regions from the open-access databases of a previous multi-country study (Gasparrini et al. 2015a). This dataset has been also made publicly available by Dr. Antonio Gasparrini on his personal web page (http://www.ag-myresearch.com/). It consists of daily counts of all-cause deaths (i.e., natural and external) and weather conditions (e.g., daily minimum and maximum temperature, 24-hour average temperature and relative humidity) in 9 regions of England and in Wales from January 1, 1993 to December 31, 2006. Specifically, daily mortality counts were summed up based on date of death and divided by government region according to the postcode of residence at the time of death, while the meteorological data were population-weighted from an average of 29 monitoring stations (range: 7 in London to 44 in Wales). A detailed description of these data can be found elsewhere (Armstrong et al. 2011; Gasparrini et al. 2012b; Gasparrini et al. 2015b). Daily DTR was then calculated by subtracting minimum temperature from maximum temperature for each Government Office Region.

2.2. Statistical analysis

The DTR-mortality association was investigated with a two-stage analytic approach using the 14-year time-series data from the ten regions in England and Wales. In the first stage, we applied a time-series regression for each region to estimate region-specific DTR-mortality associations. A second-stage multivariable meta-analysis was then conducted to pool these estimated associations at the national level. This analytic strategy has been well documented in previous publications (Gasparrini and Armstrong 2013; Gasparrini et al. 2012a).

2.2.1. First-stage time-series regression

A standard time-series generalized linear model (GLM) (Peng et al. 2006) assuming a quasi-Poisson distribution was first applied to assess region-specific DTR-mortality relationships. Distributed lag nonlinear model (DLNM) (Gasparrini 2011; Gasparrini et al. 2010) was incorporated into the GLM to model the lagged and nonlinear effects of DTR. Specifically, a flexible "cross-basis" function for DTR was defined by a combination of a natural cubic spline (NCS) with 3 internal knots (10th, 75th, and 90th) for DTR space and a NCS with 2 internal knots at equally spaced log-values for lag space. These modeling choices were motivated by previous large scale investigations (Gasparrini et al. 2015b; Guo et al. 2014). We extended the lag period to 14 days to capture the overall DTR effect since our preliminary analyses illustrated little effects after 14 days of lag.

To remove the long-term trends and seasonality of all-cause deaths, we used a NCS with 8 degrees of freedom (*df*) per year for calendar time (Gasparrini et al. 2015b). Day of the week (DOW) was included as an indicator variable to allow the short-term fluctuation (Zhang et al. 2016). Also, we controlled for the confounding effects of the current day's mean relative humidity (MeanRh), and the moving average of lag 0–14 days for mean temperature (MeanT_{0-14}) using 3 *df* NCS at equally spaced quantiles (Chen et al. 2014; Zeng et al. 2017). Hence, the GLM model is given as follows:

$$Y_t \sim \mathrm{Poisson}(\mu_t)$$

$$\mathrm{Log}(\mu_t) = \alpha + \beta DTR_{t,l} + NCS(Time_t,\ df = 14 \times 8) + \gamma DOW_t + NCS(MeanT_{0-14t}, df = 3) + NCS(MeanRh_t, df = 3)$$

where t is the day of observation ($t = 1, 2, 3, \ldots, 5113$), and Y_t is the observed daily death counts on day t; α is the intercept; $\mathrm{DTR}_{t,l}$ is the cross-

Table 1
Region-specific summary statistics for all-cause mortality, mean temperature, and mean relative humidity in England and Wales, 1993–2006.

Region	Death			Mean temperature (°C)		Mean relative humidity (%)	
	Daily average	Daily range	Total	Daily average	Range	Daily average	Range
North East	79.8	41–178	407,862	9.5	−5.3–22.6	71.6	33.5–98.7
North West	209.2	138–454	1,069,737	10.2	−6.3–25.1	74.9	27.6–99.5
Yorkshire & Humber	146.2	90–300	747,424	9.9	−4.5–23.2	75.2	33.1–99.2
West Midlands	150.9	93–310	771,704	10.1	−5.2–25.2	74.4	28.9–99.5
East Midlands	118.6	70–253	606,487	10.1	−5.0–24.0	75.5	31.3–99.8
Wales	92.3	45–181	472,014	10.4	−3.1–24.4	78.0	40.9–98.9
East	146.6	87–300	749,380	10.6	−4.1–25.3	75.1	32.6–99.6
South East	221.5	147–481	1,132,649	10.8	−4.1–25.3	76.1	37.2–99.3
South West	150.8	97–303	771,244	10.7	−3.6–24.3	78.3	38.9–99.0
London	165.3	99–363	845,215	11.7	−3.1–29.2	67.4	26.3–97.9
Overall	148.1	41–481	7,573,716	10.4	−6.3–29.2	74.7	26.3–99.8

basis matrix of DTR (t) and lag pattern (l) produced by DLNM, β is the vector of coefficients for $DTR_{t,l}$; γ is the regression coefficients for DOW.

To further investigate the seasonal pattern of the DTR-mortality association, we stratified the whole study period into three 4-month periods according to monthly mean temperatures: hot season (June to September), cold season (December to March of the next year), and transitional season (October, November, April, and May) (Guo et al. 2016). In the stratified analyses, we used 4 *df* NCS (equally spaced knots) for day of the year to describe seasonal variation within each period, and linear and quadratic terms of time to eliminate the long time trend over 14 years (Armstrong et al. 2011; Gasparrini et al. 2012b). To ease the interpretation and quantification, the effects of high DTR and low DTR for each period were respectively defined as the mortality risks of the 99th percentile relative to the 75th percentile and the 1st percentile relative to the 25th percentile in the DTR distribution.

2.2.2. Second-stage multivariable meta-analysis

As the exposure from multiple studies should be measured on the same scale when conducting the meta-analysis of exposure–response relationships, we adopted a relative scale measurement by transforming DTR to the related region-specific percentiles (Gasparrini et al. 2012a). Through selecting the internal knots at the same percentiles, such a standardization in DTR exposure measurement could make the region-specific results comparable on the same scale and facilitate the pooling of nonlinear DTR–mortality associations at the national level.

For each region, we reduced the first-stage associations to the overall DTR–mortality, (i.e., cumulative risk during the whole lag period), which was then pooled using a multivariate meta-analysis. This meta-analytical model was also used to derive the best linear unbiased prediction (BLUP) of the overall cumulative exposure-response association in each location. For lag-response associations, similar steps of parameter reduction and meta-analytical model were also performed so as to obtain region-specific and pooled lag patterns for both low and high DTR effects.

To intuitively illustrate the potential effect modification in the DTR-mortality association, we included some region-specific climatological (i.e., temperature range, annual average temperature, DTR, and humidity) and geographical factors (i.e., latitude and longitude), and compared the exposure-response curves predicted at the 90th percentile and the 10th percentile of the predictors (Onozuka and Hagihara 2017; Xiao et al. 2017). Besides, we fitted a number of multivariate meta-regression (MMR) models for quantitative evaluation of the potential modifiers. Specifically, we first established the basic MMR model with intercept only, which allowed for heterogeneity modelled through random effects. Then, we performed the single meta-predictor MMR analysis by separately incorporating the region-specific factors into the basic MMR model. Additionally, we employed a multivariate extension of likelihood ratio (LR) test and Wald test to evaluate the significance of these single meta-predictor models compared to the intercept-only model, as well as the effects of meta-predictors. Several multiple meta-predictor models were further fitted using the subsets of significant predictors identified from single meta-predictor models. All MMR models were estimated adopting the method of maximum likelihood estimation, and the residual heterogeneity was examined through the multivariate extension of I^2 statistic and tested by Cochran Q test (Gasparrini et al. 2012a). The goodness of model fits was measured using Akaike information criterion (AIC) and Bayesian information criterion (BIC).

To check the robustness of our main results, we performed some sensitivity analyses by varying the *df* (s) of some confounders (e.g., calendar time, seasonality, mean temperature, and relative humidity) and the specified lag patterns when adjusting for the delayed effects of mean temperature and relative humidity.

All the analyses were performed with R software version 3.3.2 (R Development Core Team 2016, http://www.R-project.org). The "dlnm" package was used to conduct the first-stage time-series regression and the "mvmeta" package was used to perform the second-stage meta-analysis and meta-regression. Two-sided statistical tests were conducted, and effects of $p < 0.05$ were considered statistically significant.

3. Results

3.1. Data description

Table 1 gives the descriptive statistics of daily death, mean temperature, and relative humidity for the 10 UK regions. A total of 7,573,716 persons died in England and Wales between 1993 and 2006, with a daily average of 148.1 deaths per region (ranging from 79.8 in North East to 221.5 in South East). The annual average temperature and

Table 2
Region-specific distribution characteristics of daily DTR (°C) in England and Wales, 1993–2006.

Region	Mean	Range	Percentiles						
			P_1	P_{10}	P_{25}	P_{50}	P_{75}	P_{90}	P_{99}
North East	6.6	0.8–17.6	1.7	3.2	4.6	6.4	8.3	10.4	14.3
North West	6.9	1.1–17.7	2.3	3.8	4.9	6.4	8.4	10.9	14.6
Yorkshire & Humber	7.0	0.9–17.7	1.9	3.6	4.9	6.7	8.8	11.1	14.7
West Midlands	7.7	0.8–19.6	1.7	3.7	5.3	7.4	9.7	12.4	16.5
East Midlands	7.6	1.1–19.7	2.0	3.8	5.3	7.2	9.6	12.2	16.0
Wales	6.7	1.1–15.7	2.2	3.7	4.8	6.4	8.3	10.4	13.5
East	8.0	1.0–20.2	1.9	3.9	5.6	7.7	10.1	12.6	16.2
South East	7.7	1.0–18.8	2.0	3.8	5.3	7.4	9.9	12.3	15.7
South West	7.2	1.2–16.0	2.3	4.0	5.2	6.8	9.0	10.9	13.9
London	7.1	1.0–19.1	2.0	3.6	4.9	6.8	9.0	11.2	14.8
Overall	7.3	0.8–20.2	2.0	3.7	5.1	6.9	9.1	11.4	15.0

relative humidity was 10.4 °C (range: 9.5–11.7 °C) and 74.7% (range: 67.4–78.3%), respectively. As summarized in Table 2, daily DTR varied greatly from 0.8 °C to 20.2 °C with an annual average of 7.3 °C for the included regions. A similar skewed distribution for daily DTR was observed in each region, as the number of days was very sparse for extremely high DTR (also shown in Fig. 1).

3.2. Pooled and region-specific DTR-mortality associations

Fig. 1 illustrates region-specific exposure-response curves for DTR-mortality associations along lag 0–14 days. During the whole study period, DTR extremes (both high and low DTR) exhibited a significant impact on mortality. Clear evidence of increased mortality associated with

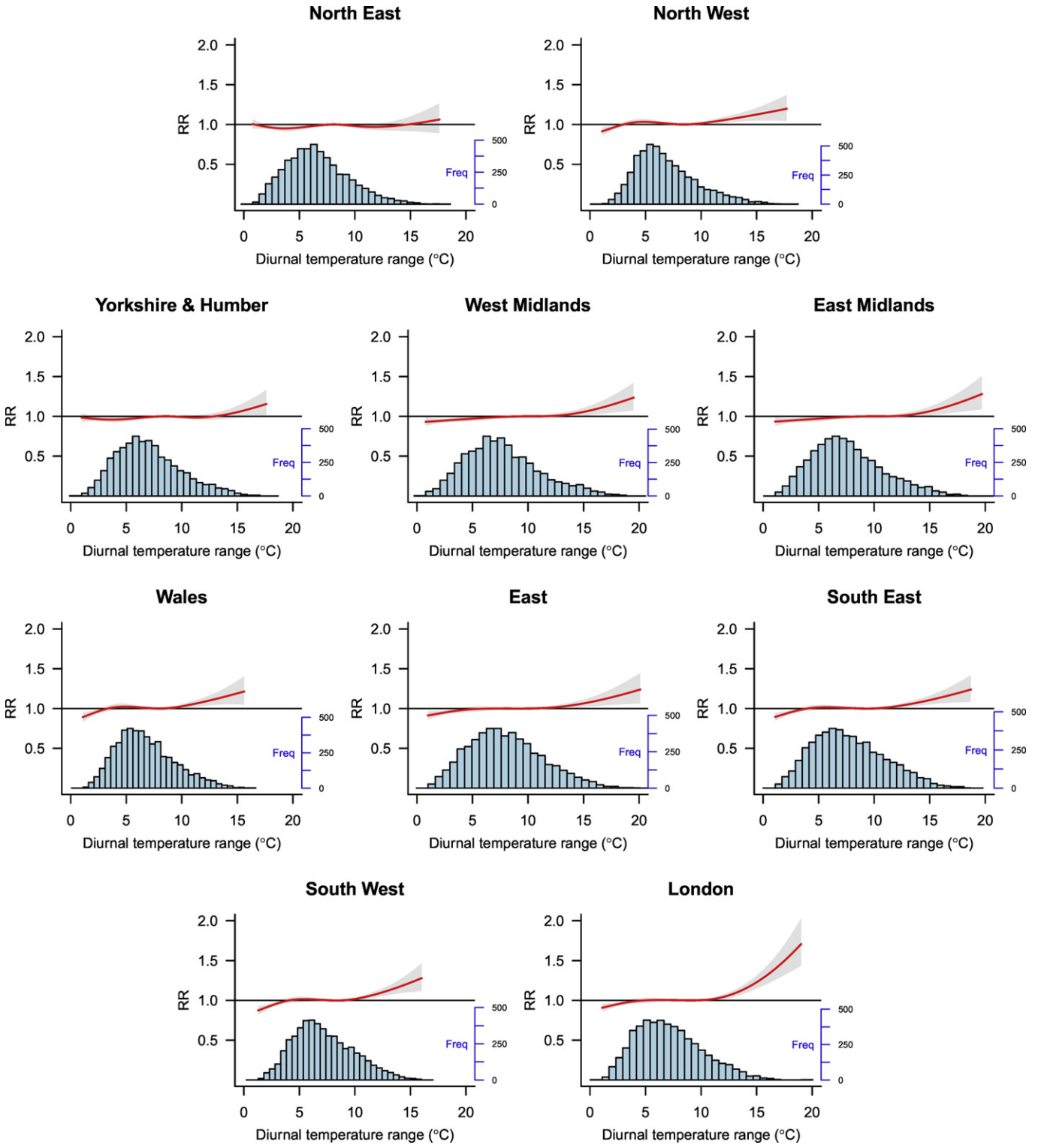

Fig. 1. DTR-mortality association predicted by BLUP and the DTR frequency distribution in each region. The continuous bold red lines represent the estimated exposure-response curves and the grey areas are the 95% confidence intervals. The reference DTR was the 75th percentile of DTR distribution for each region.

extremely high DTR was revealed for all regions except North East, whereas extremely low DTR tended to show some protective effects.

3.3. Pooled exposure-response and lag-response relationships

A pooled non-linear DTR-mortality association was identified in England and Wales, despite some subtle differences between region-specific curves (Fig. 2A). At the national level, increasing DTR raised the mortality risk observably when DTR exposure was below 25th percentile or above 90th percentile of DTR distribution, with an intermediate risk plateau indicating no associations. The adverse effect of extremely high DTR appeared immediately with a peak and decreased sharply within a lag of 3 days (Fig. 2B). Afterwards, the mortality risk weakened gradually until it kept stable around the null effect (RR = 1) after 10 days lag. Similar patterns of lag was observed for the protective effect of extremely low DTR (Fig. 2C).

3.4. Seasonal variation of DTR-mortality association

As outlined in Fig. 3, DTR-mortality associations varied greatly by season, with an approximate shape of "J" for hot season, inverted "V" for cold season, and "W" for transitional season, respectively. Compared with the whole-period analysis, hot season and transitional season exhibited generally similar curve characteristics at high DTR exposure, while the effects of high DTR increased to a peak at about 95th percentile and then dropped down quickly in cold season. As for the effects of low DTR, mortality risks showed a significant decrease in cold season but no evident changes in hot season. Contrarily, we observed suggestive evidence of increasing risk associated with extremely low DTR in transitional season.

3.5. Season-specific effect estimates of extremely high and low DTR

Figs. 4 & 5 demonstrate region-specific estimates for mortality effects of extremely high and low DTR, stratified by season. In the full-year analysis, an overall effect (RR) was 1.11 (95% *CI*: 1.06, 1.16) for high DTR and 0.95 (0.92, 0.98) for low DTR, respectively (Table S1 & S2). Hot season exhibited higher risks associated with high DTR in comparison to cold and transitional seasons (Fig. 4). At the national level, entirely different association patterns were found between low DTR and mortality when conducting season-stratified analyses (Fig. 5).

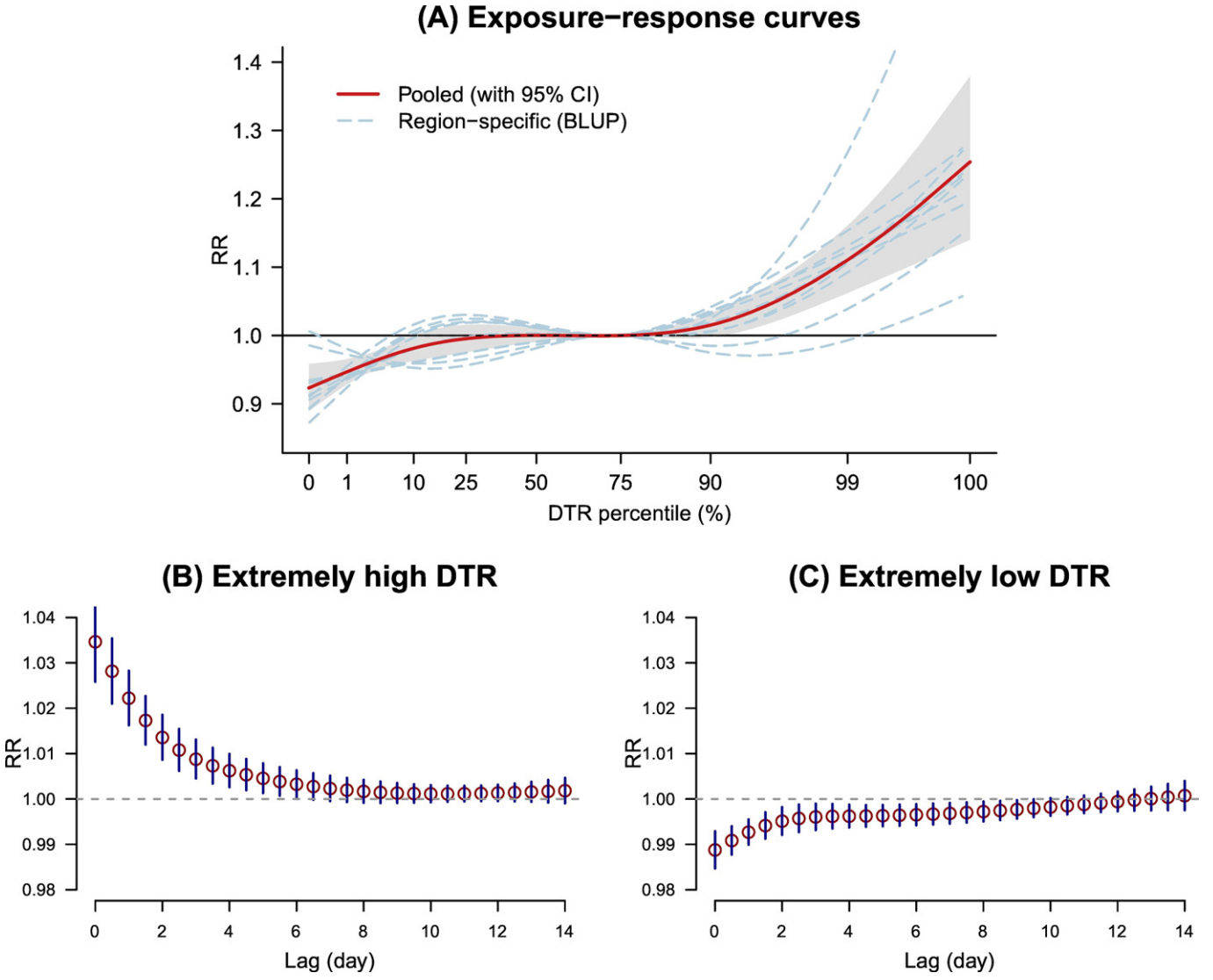

Fig. 2. Pooled exposure-response relationship and lag patterns of extremely high DTR and low DTR. The continuous bold red lines represent the pooled curves and the grey areas are the 95% confidence intervals, whereas the long-dashed light blue lines are the region-specific estimates predicted by BLUP. The effects of extremely high and low DTR was estimated at the 99th percentile relative to the 75th percentile and the 1th percentile relative to the 25th percentile, respectively.

3.6. Potential regional-level modifiers of DTR-mortality association

Table 3 demonstrates the model fits, residual heterogeneity, and significance tests for predictors between different MMR models. The intercept-only MMR model revealed a substantial residual heterogeneity when modeling DTR-mortality relationship ($Q = 121.0$, $p < 0.001$), indicating 70.2% of the total variation in the effect estimates attributable to the true differences across regions. In single-predictor MMR models with latitude, average temperature, and average humidity, we observed significantly better goodness of model fits (p-value of LR test < 0.01) and decreased I^2 statistics, which showed suggestive evidence on the potential effect modification of these predictors. Multiple-predictor models further largely reduced between-region heterogeneity, which became no more significant with the I^2 statistic decreasing to 1.0% when incorporating all the three identified predictors into the MMR model (model 4). Wald tests for significance of predictors included in MMR models were presented in Table S3.

Fig. 6 compares the DTR-mortality curves predicted at the 90th percentile and 10th percentile of meta-predictors. Intuitively, we found that low-latitude regions exhibited significantly stronger protective effects of low DTR and higher mortality risks associated with high DTR. Besides, high average temperature could strongly elevate DTR-mortality association at high DTR percentiles. As for average humidity, we observed increased risks of high DTR in less humid regions, but the effect gap was not huge enough to differentiate between-region associations with DTR. Consistent with the results presented in Table 3, no obvious modifying effects were identified for other predictors (i.e., longitude, temperature range, and average DTR).

3.7. Sensitivity analysis

The results were broadly similar when we varied the degrees of freedom for calendar time (7–10 *df* NCS per year) (Fig. S3) or used 5 *df* NCS for seasonality (Fig. S4), mean temperature (Fig. S5), and relative humidity (Fig. S6) in the analyses. Also, DTR-mortality associations changed slightly when we adjusted for the moving average of lag 0–7 days for mean temperature (Fig. S7) or lag 0–14 days for relative humidity (Fig. S8).

4. Discussion

In this nationwide investigation, we examined the association between daily DTR and mortality in England and Wales using 14-year time-series data. We found significant mortality impacts of short-term exposure to DTR extremes, with clear evidence of seasonal patterns. We additionally identified several effect modifiers of DTR-mortality relation at the regional level. Our findings would contribute to better understanding of health impact due to unstable weather, thus promoting related decision-making and optimizing health resource allocation so as to fight against and adapt to climate change across the globe.

Previously, some epidemiologic studies employed linear terms for DTR to assess its mortality effects based on prior knowledge or preliminary analysis of dose-response curve (Chen et al. 2007; Kan et al. 2007; Song et al. 2008; Zhang et al. 2017d). Increasing evidence of non-linear association was observed in recent years (Ding et al. 2015; Lim et al. 2012a; Vutcovici et al. 2014; Wang et al. 2013), consistently linking increased mortality and morbidity with high DTR exposure. Also, our

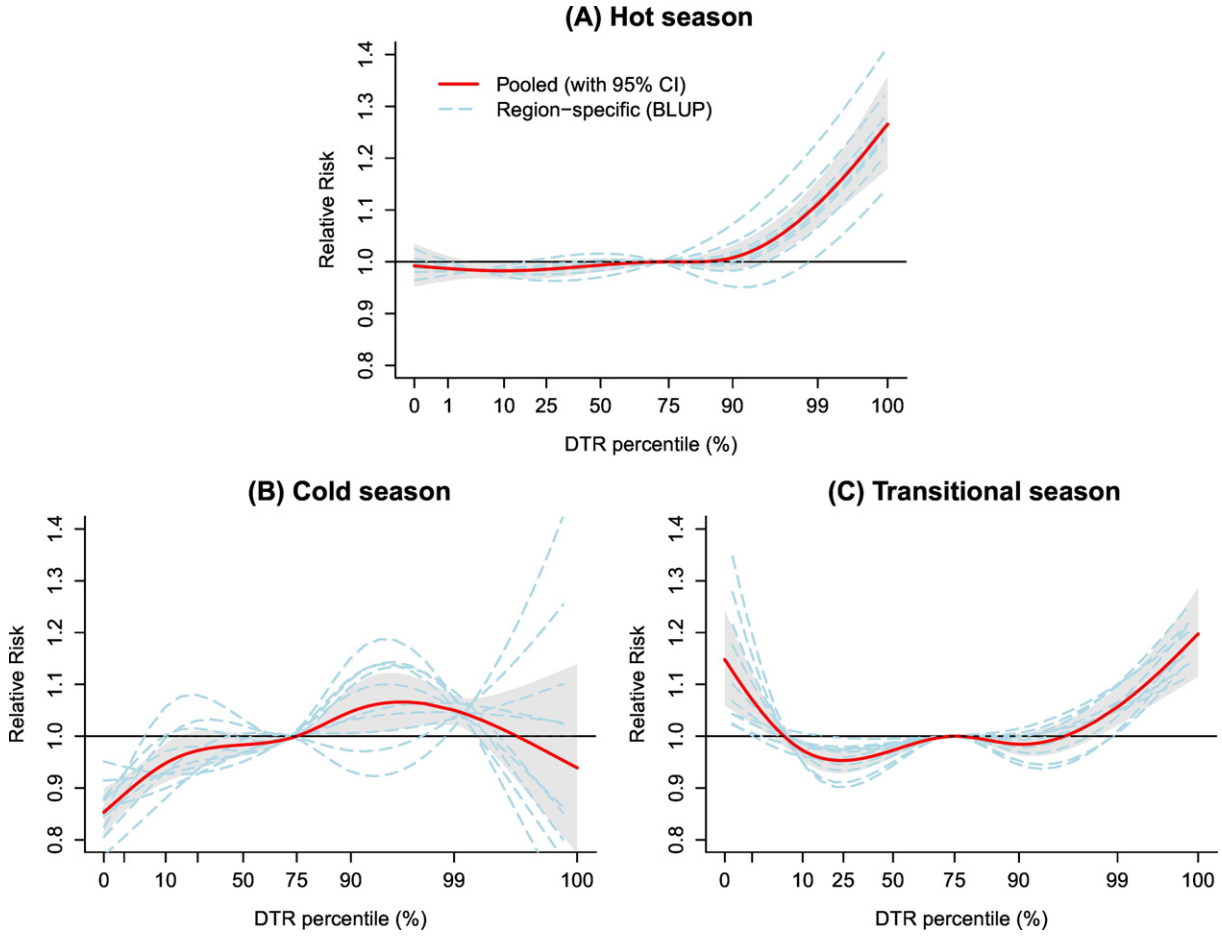

Fig. 3. Pooled and region-specific DTR-mortality association in hot season (A), cold season (B), and transitional season (C). The continuous bold red lines represent the pooled curves and the grey areas are the 95% confidence intervals, whereas the long-dashed light blue lines are the region-specific estimates predicted by BLUP. The reference DTR was the 75th percentile of DTR distribution in each period.

pooled analysis of 10 UK regions between 1993 and 2006 strengthened the nonlinear DTR-mortality association. Therefore, the linear model specification may be incompetent to capture DTR-related health effects precisely and comprehensively, although model complexity and estimation could be largely simplified.

During the whole study period, our regional and pooled analyses demonstrated clear evidence of increased mortality associated with short-term exposure to extremely high DTR, which was in accordance with several other multi-city time-series studies in America (Lim et al. 2015), Korea (Lim et al. 2012b), and China (Zhou et al. 2014). These studies reported an estimated increase in non-accidental mortality ranging from 0.18% (95% *CI*: 0.09–0.28%) to 0.5% (0.3–0.7%) associated with a 1 °C increase in DTR. The effect magnitudes of DTR on mortality estimated in our study may not be comparable to those from prior studies, as we adopted different analytic strategies and observed rapid mortality increase only at extremely high DTR (above 90th percentile). Similar effect pattern of high DTR with potential threshold was also observed in a high-plateau city of southwest China, indicating a comfort DTR zone with plateauing mortality risks (Ding et al. 2015). Nevertheless, the above study did not show any protective effect of extremely low DTR on total mortality, as was clearly identified in our study (Fig. 2A). The underlying mechanism remained unclear for between-study differences in DTR-mortality associations, while could be potentially related to several modifying factors such as population vulnerability, infrastructural development, socioeconomic status, and long-term climate conditions (Cheng et al. 2014; Kim et al. 2016; Lim et al. 2012b).

Generally, cold season brought more daily deaths than warm season. A number of recent studies have examined the seasonal variations of DTR-health relation, while the reported results were not so consistent. The pooled analysis of a Chinese multi-city study (Zhou et al. 2014) found much stronger associations of DTR with cause-specific mortality during the cold season than during the warm season, in spite of the opposite finding in Xi'an city. In Hong Kong, besides, Tam et al. (Tam et al. 2009) explored the joint effects between DTR and season on cardiovascular mortality among the elderly, by comparing the mortality risks in cold season relative to warm season. The estimated ratios of RR at different lag days ranged from 1.100 (1.065–1.136) to 1.105 (1.070–1.141), indicating significantly higher DTR effects in cold season. However, in another time-series investigation conducted in six Korean metropolitan areas during 1992–2007 (Lim et al. 2012b), a 1 °C increase of DTR was linked with significant mortality increases of 0.7% (0.2–1.1%) in summer and 0.8% (0.5–1.2%) in autumn, but no associations were identified in winter (0.2%, −0.3–0.8%) and spring (0.2%, −0.1–0.5%). In the present study, hot season exhibited generally stronger positive association of mortality with extremely high DTR compared with cold and transitional seasons. Interestingly, entirely different association patterns were observed in the season-stratified analyses for extremely low DTR, with the adverse effect identified in transitional season. Additionally, both extremely low and high DTR increased non-accidental mortality in Guangzhou, China, and cold season enhanced the DTR extremes-mortality association (Luo et al. 2013). Up to date, these discrepant findings regarding seasonal modification are difficult to understand due to the very sparse knowledge. Further comprehensive epidemiologic studies are still largely needed worldwide to investigate the underlying reasons for the great variation in season-specific DTR-mortality relationships.

Some individual-level modifiers of DTR-mortality association have been examined in previous investigations (Cheng et al. 2014). In agreement with most temperature-mortality studies, females, the elderly, and those with low socioeconomic status were generally identified as the vulnerable subgroups to high DTR exposure (Ding et al. 2016; Yang et al. 2013). Besides, there was also emerging evidence showing that regional characteristics could modify DTR-mortality association (Kim et al. 2016). In the present study, greater DTR effects were observed in regions with higher average temperature, decreased humidity, and lower latitudes. The modifying effects of these climatological and geographical factors strengthened previous DTR-mortality findings indicating great variation by locations (Cheng et al. 2016; Kim et al. 2016). The notable finding of enhanced mortality effects of high DTR

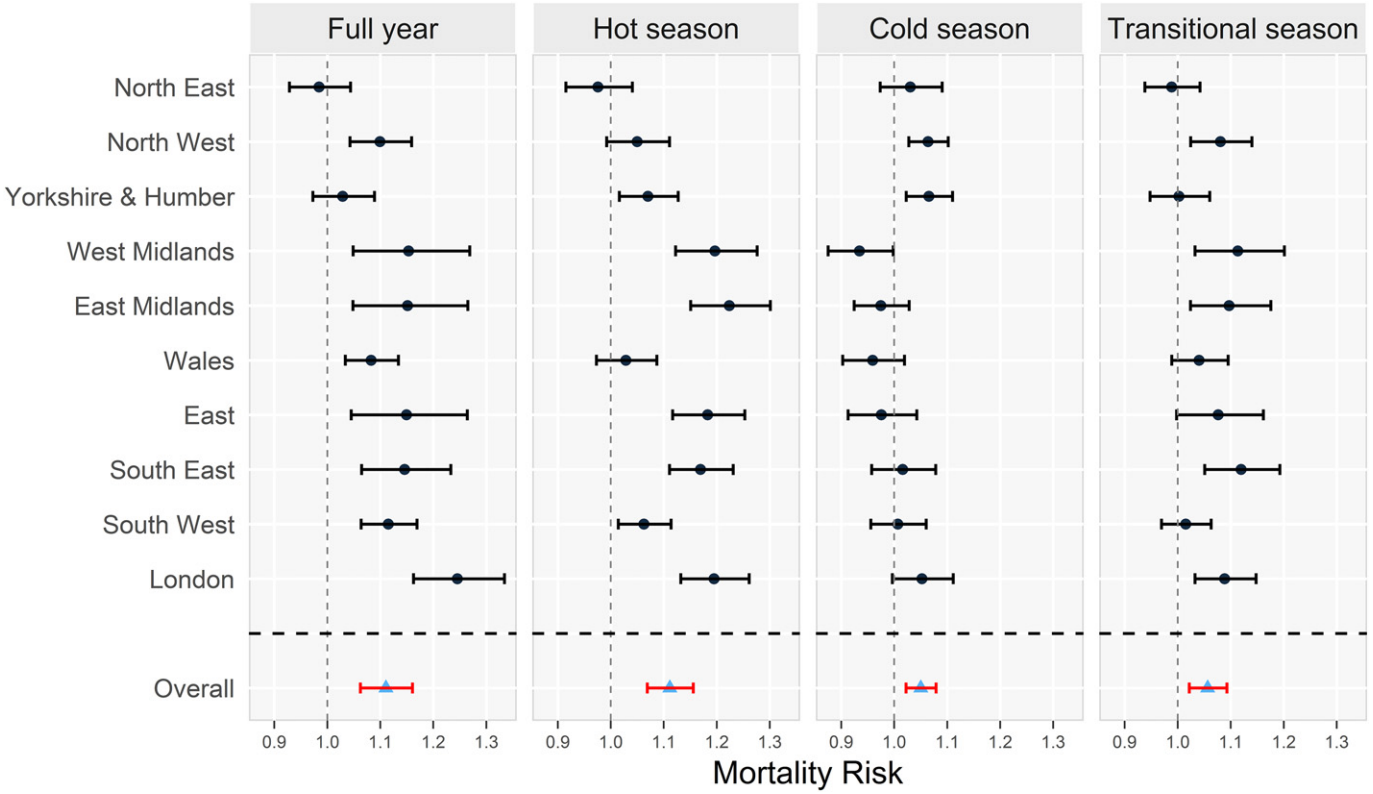

Fig. 4. Region-specific and overall effect estimates of extremely high DTR on mortality (RR with 95% *CI*).

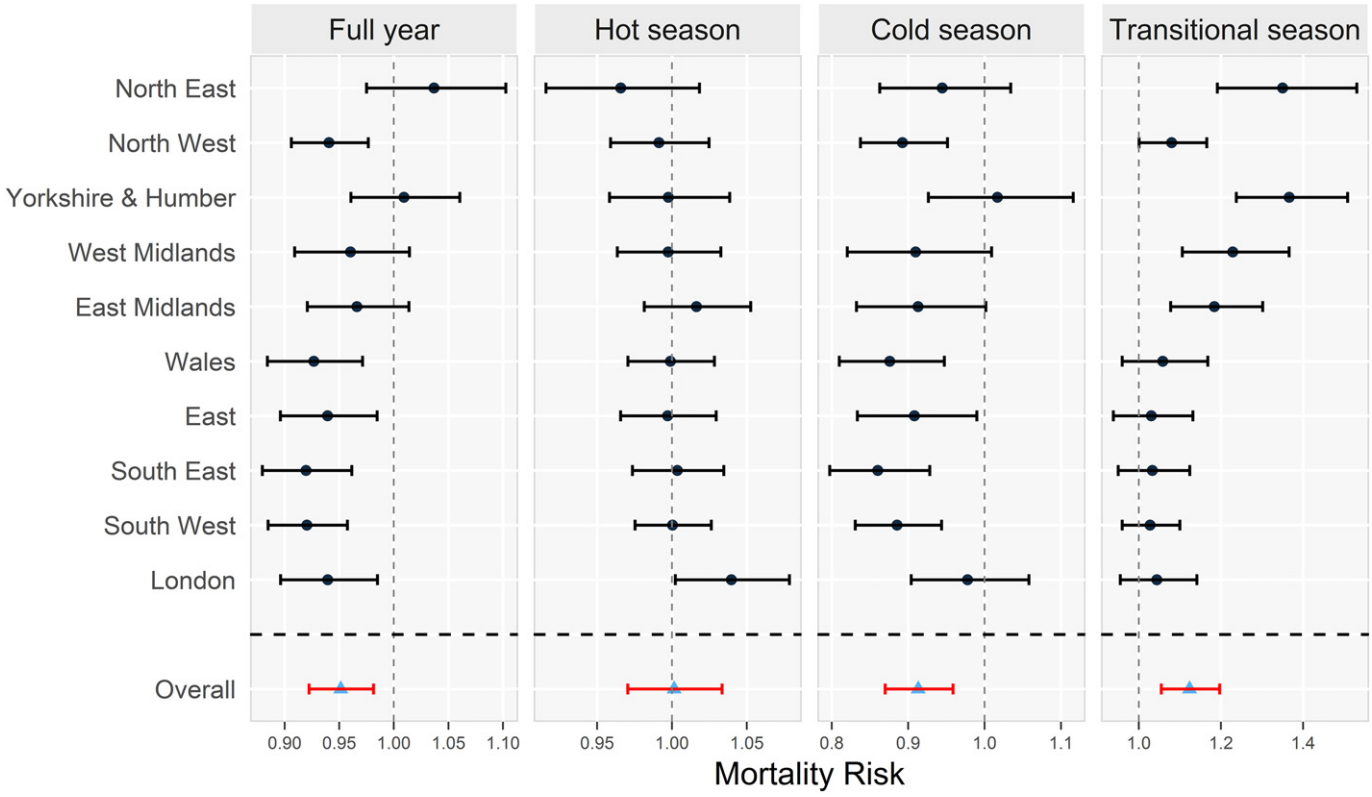

Fig. 5. Region-specific and overall effect estimates of extremely low DTR on mortality (RR with 95% *CI*).

in warmer regions echoed to a previous cohort study in 135 US cities investigating the relation between summer temperature variability and long-term survival among elderly people (Zanobetti et al. 2012). Despite the fact that no clear evidence was available for the interactive effects of temperature and humidity with DTR, we speculated that it might be partly related to the long-term biological adaptation to local weather conditions (i.e., acclimatization), which was associated with population vulnerability to weather extremes (Gasparrini et al. 2015b; Guo et al. 2014). With regard to latitude of a region/city, low latitude tended to reduce heat vulnerability (Xiao et al. 2015) while it was generally associated with increased average temperature. Thus, the jointed effects of low latitude and high temperature seemed to be mutually illustrated in this study.

In addition to climatological and geographical factors, several large-scale investigations also showed that city-level demographical (e.g., the proportion of the elderly), infrastructural (e.g., health care service), and socioeconomic characteristics (e.g., urbanization level, average education level) may modify temperature-related health effects (Chen et al. 2016; Huang et al. 2015; Ma et al. 2015b). As noted in our meta-regression analyses, however, the three meta-predictors accounted for the large majority of between-region heterogeneity in England and Wales. This over-explanation in heterogeneity could be largely attributable to the initial aggregation of climate and mortality data to the regional scale, which have counteracted the tenuous differences existing between included cities in this study. Further efforts in this field should focus on more fine-scale spatial DTR-health analysis across the globe through examining more diverse city-level characteristics, so as to lead a comprehensive understanding of the relative contribution rates for these identified modifiers.

Our work has significant public health implications. As widely accepted, annual average DTR decreased on a global scale during the second half of the 20th century. In most European regions/countries,

Table 3
Model evaluation and parameter test for different multivariate meta-regression models.

Meta-regression models	Model fit		Cochran *Q* test			I^2 (%)	LR test for model[a]	Wald test for predictor[a]
	AIC	*BIC*	*Q*	*df*	*p*-Value			
Intercept-only	−75.9	−52.2	121.0	36	<0.001	70.2	–	–
Single-predictor								
Latitude	−85.0	−54.6	79.2	32	<0.001	59.6	0.002	<0.001
Longitude	−71.6	−41.2	115.5	32	<0.001	72.3	0.449	0.367
Average temperature	−91.1	−60.7	70.5	32	<0.001	54.6	0.001	<0.001
Temperature range	−74.8	−44.4	106.2	32	<0.001	69.9	0.142	0.065
Average DTR	−73.6	−43.2	109.4	32	<0.001	70.7	0.219	0.130
Average humidity	−83.7	−53.3	107.3	32	<0.001	70.2	0.003	<0.001
Multiple-predictor								
Model 1 (Lat + Tmean)	−96.2	−59.0	54.9	28	0.002	49.0	<0.001	–
Model 2 (Lat + Rh)	−94.4	−57.2	57.0	28	0.001	50.9	<0.001	–
Model 3 (Tmean + Rh)	−99.0	−62.0	42.8	28	0.036	34.6	<0.001	–
Model 4 (Lat + Tmean + Rh)	−104.2	−60.3	21.8	24	0.590	1.0	<0.001	–

Lat, latitude; Tmean, average temperature; Rh, average humidity.
[a] Indicates *p*-value of the test.

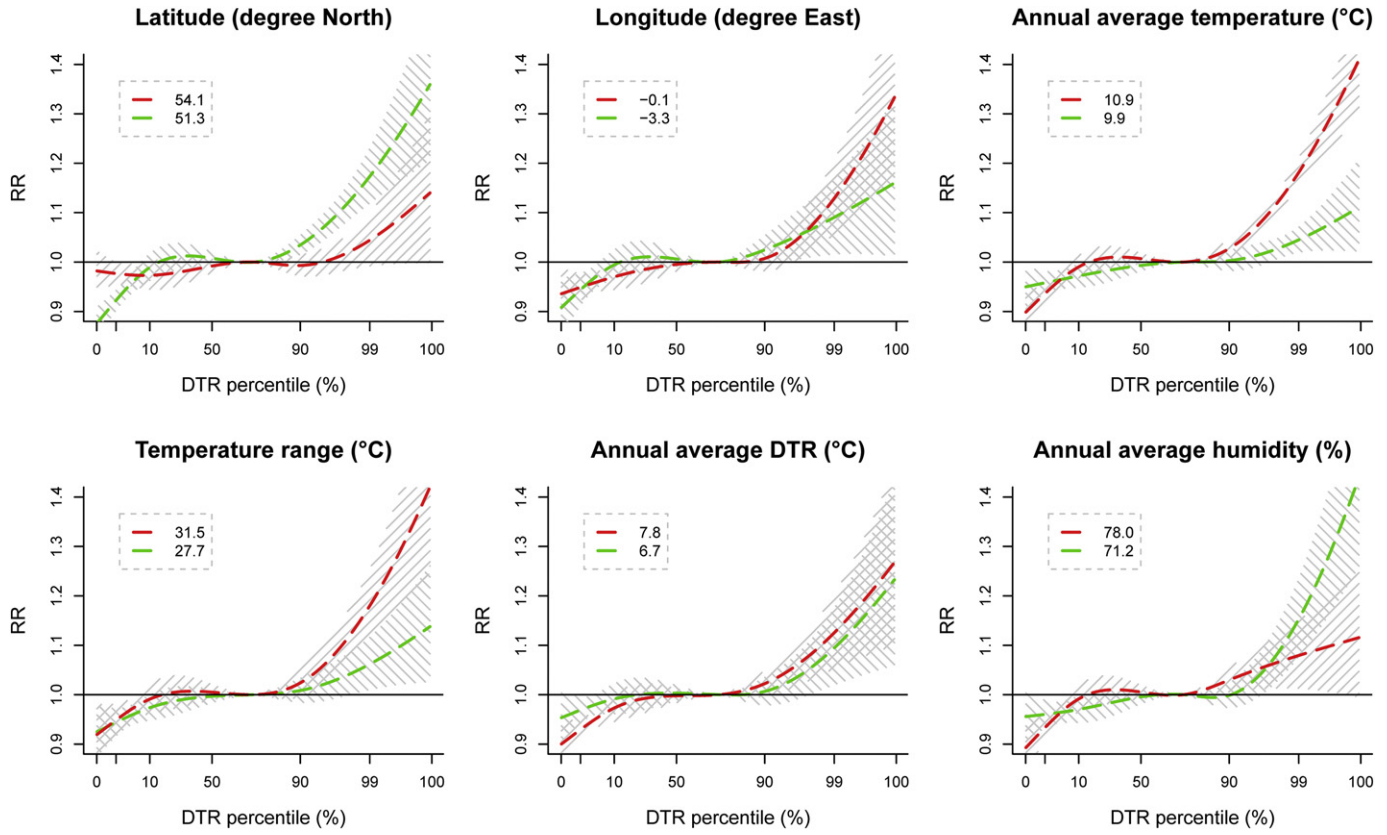

Fig. 6. DTR-mortality associations predicted at the 90th percentile (red) and 10th percentile (green) of included meta-predictors. The grey shaded areas with diagonal lines on the upper left and bottom right represented the estimated 95% confidence intervals of high and low meta-predictor percentiles, respectively. All the exposure-response curves were centered at the 75th percentile of DTR distribution.

however, it has reversed from a decrease to an increase in recent decades (Makowski et al. 2008). Our findings from England and Wales highlighted the need to comprehensively evaluate DTR-related health burden (e.g., mortality) in Europe, which has been relatively more studied in East Asia and North America (Cheng et al. 2014; Kim et al. 2016; Lim et al. 2015). Using modern multivariable meta-analytic techniques, the present study identified several regional-level characteristics that may modify the nonlinear DTR-mortality association. Further well-designed investigations on both community- and individual-scale effect modification, would be of great practical importance for public health decision-making to protect the susceptible populations and vulnerable communities.

Several limitations of this study should be acknowledged. First, there may exist some evitable biases when assessing DTR-mortality associations using an ecological study design (Gasparrini and Armstrong 2010). Second, in our main analyses, we failed to account for the potential mediating, confounding or modifying effects of air pollution due to data unavailability. However, there was also epidemiologic evidence showing that temperature/DTR-mortality associations would be scarcely affected with and without adjusting for air pollution (Anderson and Bell 2009; Chen et al. 2015; Lim et al. 2015). Additionally, we only investigated all-cause mortality in relation to DTR, as age- or cause-specific mortality was not included in the dataset.

5. Conclusions

In summary, our study identified a non-linear DTR-mortality relationship in UK, and added strong evidence that extremely high DTR increased short-term mortality. Also, the effects of extremely high and low DTR exhibited great differences in seasonal patterns. Regional latitude, average temperature and humidity were found to modify DTR-mortality association, with increased vulnerability to extremely high DTR in low-latitude, warmer, and less humid regions. In the context of global climate change, these findings may have some important implications in decision-making and resource allocation for the public health authorities.

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Author contributions

Yunquan Zhang and Chuanhua Yu conceived and designed the experiments; Yunquan Zhang collected the data, performed the data analysis, and drafted the manuscript. Minjin Peng and Lu Wang helped revise the manuscript. All authors read and approved the final manuscript.

Conflicts of interest

The authors declare they have no competing financial interests.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.scitotenv.2017.11.056.

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